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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,268	02/19/2004	Foe S. Tjoeng	1327/01	4226

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,268	TJOENG, FOE S.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-5,11-14,16 and 19* is/are allowed.

6)☒ Claim(s) *6-9 and 20-29* is/are rejected.

7)☒ Claim(s) *10,15,17 and 18* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20050912*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

SD

1. Claims 6, 8, 9, 15, 17, 18, and 20-29 are objected to because of the following informalities: At claim 6, line 1, and claim 15, line 1, "the step" should be inserted after "comprising". At claim 9, line 3, and claim 18, line 3, "protein" should be changed to "peptide or protein" so as to be consistent with the reactants recited at line 2 of each claim. At claims 23-26, line 1 of each claim, "of" should be deleted from after "comprising". Appropriate correction is required.

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

For the purposes of this invention, the level of ordinary skill in the art is deemed to be at least that level of skill demonstrated by the patents in the relevant art. Joy Technologies Inc. v. Quigg, 14 USPQ2d 1432 (DC DC 1990). One of ordinary skill in the art is held accountable not only for specific teachings of references, but also for inferences which those skilled in the art may reasonably be expected to draw. In re Hoeschele, 160 USPQ 809, 811 (CCPA 1969). In addition, one of ordinary skill in the art is motivated by economics to depart from the prior art to reduce costs consistent with desired product properties. In re Clinton, 188 USPQ 365, 367 (CCPA 1976); In re Thompson, 192 USPQ 275, 277 (CCPA 1976).

3. Claims 6, 8, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Zalipsky (U.S. Patent No. 5,122,614). Zalipsky teaches reacting a PEG active ester, PEG-O-C(O)-O-succinimide, with the amino group of a protein to form PEG conjugated to the protein through a

urethane linkage. The PEG-protein conjugates have reduced immunogenicity and antigenicity and have a longer lifetime in the bloodstream, and are used therapeutically. See, e.g., column 4, line 63 - column 5, line 6, and column 6, Scheme 2. Zalipsky's PEG-O-C(O)-O-succinimide has the same structure as the PEG active ester produced by Applicant's claim 2. While Zalipsky's PEG-O-C(O)-O-succinimide/PEG active ester is not produced according to the same method steps recited in instant claim 2, this difference does not distinguish over Zalipsky because Applicant's claim 6 defines the PEG active ester in product-by-process format. Even a novel and unobvious process does not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

4. Claim 9 is rejected under 35 U.S.C. 103(a) as being obvious over Zalipsky (U.S. Patent No. 5,122,614). Application of Zalipsky is the same as in the above rejection of claims 6, 8, and 23. Zalipsky does not teach Applicant's claimed molar ratio of active ester to peptide or protein. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal active ester to peptide or protein ratios for the conjugation reaction of Zalipsky because reactant ratio and degree of conjugation are art-recognized result-effective variables which are routinely determined and optimized in the conjugation arts.

5. Claims 20-22 and 24-29 are rejected under 35 U.S.C. 103(a) as being obvious over Zalipsky (U.S. Patent No. 5,122,614) as applied against claims 6, 8, and 23 above, and further in view of Athwal et al (U.S. Patent Application Publication 2002/0151682). Zalipsky teaches forming PEG conjugates with proteins in general, but does not teach forming PEG conjugates with the particular proteins recited in instant claims 20-22. Athwal et al teach hTNF40-based

Fab which is modified with polyethylene glycol. The modified antibody is used to treat diseases mediated by TNFα, such as rheumatoid arthritis. See, e.g., the Abstract; paragraph [0234]; and claims 1, 15, 28, and 32. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the pegylated conjugates of Zalipsky using the hTNF40-based Fab of Athwal et al because the pegylation method of Zalipsky is not limited to any particular protein, because Athwal et al teach the desirability of pegylating hTNF40-based Fab, and because the pegylation method of Zalipsky would have been expected to be effective in pegylating the hTNF40-based Fab of Athwal et al.

6. Claims 7, 8, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Greenwald et al (U.S. Patent No. 6,180,095). Greenwald et al teach reacting a PEG active ester, PEG-O-C(O)-O-succinimide, with the amino group of a linker to form PEG conjugated to the linker through a urethane linkage. The linker is then reacted with the amino group of a drug, e.g., proteins, peptides, and immunoglobins, to form a PEG-linker-drug conjugate. The PEG-linker-protein conjugates have extended half-lives, and are used therapeutically. See, e.g., Figure 6; column 4, lines 20-35; column 17, lines 22-67; and column 23, lines 17-63. Greenwald et al's PEG-O-C(O)-O-succinimide has the same structure as the PEG active ester produced by Applicant's claim 2. While Greenwald et al's PEG-O-C(O)-O-succinimide/PEG active ester is not produced according to the same method steps recited in instant claim 2, this difference does not distinguish over Greenwald et al because Applicant's claim 7 defines the PEG active ester in product-by-process format. Even a novel and unobvious process does not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

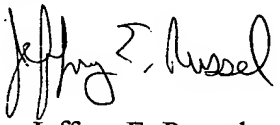
7. Claim 9 is rejected under 35 U.S.C. 103(a) as being obvious over Greenwald et al (U.S. Patent No. 6,180,095). Application of Greenwald et al is the same as in the above rejection of claims 7, 8, and 23. Greenwald et al do not teach Applicant's claimed molar ratio of active ester to linker. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal active ester to linker ratios for the conjugation reaction of Greenwald et al because reactant ratio and degree of conjugation are art-recognized result-effective variables which are routinely determined and optimized in the conjugation arts.

8. Claims 20-22 and 24-29 are rejected under 35 U.S.C. 103(a) as being obvious over Greenwald et al (U.S. Patent No. 6,180,095) as applied against claims 7, 8, and 23 above, and further in view of Athwal et al (U.S. Patent Application Publication 2002/0151682). Greenwald et al teach forming PEG conjugates with proteins and immunoglobins in general, but does not teach forming PEG conjugates with the particular proteins recited in instant claims 20-22. Athwal et al teach hTNF40-based Fab which is modified with polyethylene glycol. The modified antibodie is used to treat diseases mediated by TNFα, such as rheumatoid arthritis. See, e.g., the Abstract; paragraph [0234]; and claims 1, 15, 28, and 32. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to form the pegylated conjugates of Greenwald et al using the hTNF40-based Fab of Athwal et al because the pegylation method of Greenwald et al is not limited to any particular protein, because Athwal et al teach the desirability of pegylating hTNF40-based Fab, and because the pegylation method of Greenwald et al would have been expected to be effective in pegylating the hTNF40-based Fab of Athwal et al.

9. Claims 1-5, 11-14, 16, and 19 are allowed. Claim 10 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 15, 17, and 18 would be allowable if rewritten or amended to overcome the claim objections set forth in this Office action. The prior art of record does not teach or suggest activating PEG or a PEG-linker with N,N'-disuccinimidyl oxalate or with 1,1'-bis[6-(trifluoromethyl)benzotriazolyl] oxalate, nor does the prior art of record teach or suggest a reaction intermediate having the structure PEG-O-C(O)-O-1-[6-trifluoromethyl)benzotriazolyl].

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel
September 21, 2005